

Remarks

Claims 32, 35, 37 and 38 have been amended. Claim 33 has been canceled. New claims 39-43 have been added.

The amendments to claim 32:

- (a) separate the additives of the recited formulation into two groups (one group that does not easily induce decomposition of the benzamide derivatives and one group that stabilizes the benzamide derivatives), and
- (b) delete two additives from the lists.

Support for amendment (a) may be found in the specification at, for example, page 2, lines 32-36.

The amendment to claim 35 better defines the claimed invention.

The amendment to claims 37 and 38 makes them multiple dependent claims.

New claims 39-43 find support throughout the specification and mirror the currently pending claims 32 and 34-37. More specifically, claim 39 restricts the formulation to a solid formulation and restricts the benzamide derivative to the compound of formula (3).

No new matter has been introduced by any of the amendments. After entry of the amendments, claims 32 and 34-43 will be pending.

1. Rejection under 35 U.S.C. § 103(a)

A. Suzuki

The Examiner maintains his rejection of claims 32, 33 and 35-38 under 35 U.S.C. § 103(a) as being unpatentable over EP 0847992 to Suzuki *et al.* ("Suzuki") and again cites claim 14 of Suzuki as teaching one of the benzamide derivatives claimed by Applicants. The Examiner also states that Suzuki teaches that the described benzamide derivatives may be used in general pharmaceutical compositions and formulations. More specifically, the Examiner cites page 36, lines 5-39 in asserting that Suzuki teaches the use of, for example, calcium carbonate, amino acids, methyl celluloses, calcium carmellose, lactose, sugars, stearates, talc, polyethylene glycol and sodium alginate. According to the Examiner, the use of these excipients in combination with Applicants' claimed benzamide derivatives would have been obvious to one of ordinary skill in the art with a reasonable expectation of success.

Applicants continue to disagree with the Examiner's application of Suzuki to Applicants' claimed invention. A skilled artisan would not be motivated to choose the particular combination of additives from groups (ii) and (iii) as recited in claim 32 as amended because Suzuki does not remotely teach or suggest the unexpected properties of these additives as discovered by Applicants – *i.e.* the fact that the additives of group (ii) do not easily induce the decomposition of the recited benzamide derivatives or

pharmaceutically acceptable salts thereof, or that the additives of group (iii) stabilize said benzamide derivatives or pharmaceutically acceptable salts thereof. In fact, the inclusion in Suzuki of additives which Applicants have shown to undesirably accelerate the degradation of benzamide derivatives (*e.g.*, crystalline cellulose, lactose and polyethylene glycol), provides further evidence that Suzuki does not contemplate Applicants' invention. Without this motivation, Suzuki is reduced to nothing more than teaching random combinations of additives that encompass literally hundreds of possible compositions. The court in *In re Rouffet* held that without a motivation to combine, a rejection based on a *prima facie* case of obviousness was improper (see *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998)). In this instance, the Examiner has improperly arrived at Applicants' invention through hindsight analysis using Applicants' disclosure as a guide in picking and choosing particular additives from the broad lists of excipients and classes of excipients described in Suzuki. Because the Examiner has not provided any supporting reference(s) that would empower a skilled artisan to make a rational decision in selecting from the excipients in Suzuki to produce Applicants' claimed compositions, Applicants respectfully request that this rejection be withdrawn.

B. Suzuki in view of the International Cosmetic Ingredient Dictionary and Handbook

Claims 32-34 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Suzuki in view of the International Cosmetic Ingredient Dictionary and Handbook ("Dictionary"). According to the Examiner, Suzuki teaches the inclusion of many well-known pharmaceutical excipients with the described benzamides, but does not teach the specific excipients claimed by Applicant (*e.g.*, hydroxypropyl cellulose or mannitol or the amino compound or organic and inorganic salts). The Examiner maintains his reliance on the Dictionary for teaching these specific excipients and asserts that, absent a clear showing of unexpected results attributable to Applicants' specific selection, one of ordinary skill in the art would have been motivated to include these excipients in the Suzuki formulations with a reasonable expectation of success.

Regarding the use of the Dictionary for teaching the use of excipients not taught or suggested by Suzuki, it is clear that the Dictionary does not remedy the deficiencies present in Suzuki because the Dictionary also does not provide any motivation for a rational selection of additives based on stability-enhancement. Like Suzuki, the Dictionary simply itemizes several classes of excipients as suitable without any teaching or suggestion that certain compounds within the same class may adversely affect the stability of the benzamide derivatives. For example, neither Suzuki nor the Dictionary differentiate between partly pregelatinized starch, which stabilizes benzamide derivatives, and corn starch, which

Applicants have shown to destabilize the same derivatives. Applicants, however, have unexpectedly discovered that specific additives enhance the stability of benzamide derivatives.

The Examiner asserts that several inorganic compounds listed in the Dictionary, such as sodium bicarbonate and disodium phosphate are pH adjusters and would therefore be commonly used by a skilled artisan in altering the pH of selected compositions.

Applicants have demonstrated that several inorganic and amino compounds enhance the stability of benzamide derivatives. If pH were the only factor involved in stability, then the benzamides of formula (1), which themselves are amino compounds, would not degrade in formulations with neutral excipients such as lactose. Table 1 shows that this is clearly not the case. Therefore, it would appear that the inorganic and amino compounds are operating to stabilize benzamides by mechanisms other than pH adjustment. Applicants bring to the Examiner's attention the exemplary compositions in Table 2 which show the presence of inorganic bases such as sodium bicarbonate, potassium carbonate and sodium carbonate in amounts sufficient to stabilize the benzamide derivatives but not sufficient to significantly affect pH. As such, a skilled artisan would have little motivation to use these inorganic compounds.

Lastly, the Examiner's combining of Suzuki with the Dictionary increases the possible combinations of additives to encompass thousands of compositions instead of hundreds. Again, there is no suggestion in either Suzuki or the Dictionary to select the claimed additives or their unexpected benefits in improving the stability of the claimed benzamide compositions. For at least these reasons, Applicants therefore respectfully request that this rejection also be withdrawn.

The Examiner questions the criticality of Applicants' product produced by a dry granulation process as recited in dependent claim 37 since, according to the Examiner, a skilled artisan would avoid a wet granulation process if moisture leads to degradation of the active agent. Applicants point the Examiner to, for example, page 2, lines 1-9, as teaching that degradation of the benzamide derivatives is not due simply to hydrolysis. In Table 1, the control indicated as "None" contains only the benzamide derivative and no additives, and is shown to be stable to conditions of 40° C and 75% relative humidity for 3 months. If decomposition of the benzamide derivative were simply due to hydrolysis, it would have decomposed under these conditions. The fact that it does not demonstrates that the degradative process involves more than mere exposure to moisture. Since decomposition is clearly not simply the result of hydrolysis, a skilled artisan would not be motivated to use dry granulation to prepare the claimed compositions.

The Examiner also finds unpersuasive Applicants' earlier filed explanation of the unexpected benefits of the use of Applicants' claimed additives in stabilizing benzamide derivatives. Specifically, the

Examiner points out that an analysis of the results shown in Table 1 indicates little difference between the control value of 0.18 (*i.e.*, the benzamide derivative alone) and the values attributed to stability-enhancing additives such as mannitol (0.21), hydroxypropyl cellulose (0.20) and magnesium stearate (0.22). The Examiner further noted that it was unclear whether the claimed additives behaved identically with all the claimed compounds of formula (I).

Regarding the unexpected benefits of Applicants' compositions in stabilizing benzamide derivatives, the Examiner has erred in his analysis of the results shown in Table 1. The Examiner has recognized that the data in Table 1 demonstrates that the control value of 0.18 (*i.e.*, the benzamide derivative alone) and the values attributed to the stability-enhancing additives are the same. The Examiner, however, then asserts that there are no unexpected results because of this lack of difference in values. The Examiner has incorrectly considered the data. The fact, recognized by the Examiner, that the control value and the values for the stability-enhancing additives are the **same is the unexpected result**. Applicants point to page 1, lines 27-36 of Applicants' specification which states that "though the benzamide derivatives and pharmaceutically acceptable salts thereof of the present invention are stable per se, they become unstable and decompose markedly over time when combined with [select] additives" commonly used in dosage forms (emphasis added). Therefore, the control value, which represents the benzamide alone, is indicative of a stable condition. The fact that there is no significant difference between the control value and the values for, for example, mannitol (0.21), hydroxypropyl cellulose (0.20) and magnesium stearate (0.22) as shown in Table 1 (as the Examiner noted), is proof of the stabilizing effects of these additives under both air-tight and open-air conditions as opposed to the comparatively large values for other additives such as lactose (0.55), corn starch (0.39) and titanium dioxide (1.75), which indicate substantial degradation of the benzamide derivatives.

2. **Obviousness-Type Double Patenting**

A. **U.S. Patent No. 6,638,530**

Claims 32-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,638,530 ("the '530 patent"). The Examiner states that Applicants' claims are drawn to a combination of the benzamide derivative of formula (1) with an amino compound (*e.g.*, glycine) and a solvent which is polyethylene glycol. The Examiner also asserts that according to Applicants' claim 38, the formulation is pH adjusted, meaning that a mineral acid is present (citing Example 5 for support). According to the Examiner, claims 1-3 of the '530 patent are drawn to a combination of the same benzamide derivatives with amino compounds

(e.g., glycine hydrochloride) and a mineral acid, thus placing them within the scope of the claims of the subject application.

B. U.S. Patent No. 6,174,905

Claims 32-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-32 of U.S. Patent No. 6,174,905 ("the '905 patent"). The Examiner asserts that claims 28-32 of the '905 patent recite benzamide derivatives encompassing Applicants' benzamides with identical excipients.

In order to expedite the prosecution of this application to allowance, Terminal Disclaimers are being filed herewith relative to the issued claims of U.S. Patent No. 6,638,530 and to the issued claims of U.S. Patent No. 6,174,905, thereby overcoming the grounds for these rejections. The filing of these Terminal Disclaimers should not be interpreted or construed as an acknowledgment that any claims of the present application or of these patents are unpatentable, one over another.

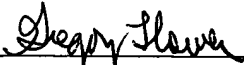
3. Conclusion

Upon consideration of the foregoing, it will be recognized that Applicants have fully and appropriately responded to all of the Examiner's rejections. Accordingly, all claims are believed to be in proper form in all respects and a favorable action on the merits is respectfully requested. The Examiner is invited to contact the undersigned with any questions or concerns that may prevent this requested allowance.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

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